A marked-up version of the claim amendments is appended hereto.

REMARKS

Claims 37-72 are pending.

Rejections under 35 U.S.C. § 101

The Examiner has rejected Claims 37-54 under 35 U.S.C. § 101 as unpatentable for being directed to non-statutory subject matter. (OA at p. 2.) As amended, claims 37-54 recite "computer readable media having data structures stored thereon, the media comprising a data structure to store..." Support for the amendments can be found throughout the application including page 2, line 28; page 5, line 27; page 6, lines 8-17; page 7 lines 7-8; page 8, line 1; page 14, lines 15-16; page 14, lines 23-24; and page 15, lines 12-13. No new matter was added by these amendments.

Applicant believes that the Examiner agreed to withdraw her § 101 rejections of claims 37-54 in view of the claim amendments.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 37-54 under 35 U.S.C. § 112, first paragraph, as unpatentable for lacking an enabling disclosure. The Examiner asserted that "[c]laim 37 lacks a clear and concise recipe for parameter generation to obtain the claimed simulated metal ion" and that "[t]he specification as filed does not present a clear and direct explanation as to how the stated parameters are to be selected from a molecule to be used for designing simulated polyhedron-metalloprotein." (OA at p. 3.)

Applicant traverses these rejections. The instant specification contains and teaches the manner and process of making and using the claimed invention. A patent application is presumptively enabled. It is incumbent upon the Examiner to explain why she doubts the truth or accuracy of the statements in a disclosure. Further, the Examiner must back up her assertions with acceptable evidence or reasoning that is inconsistent with the contested statements. MPEP § 2164.04.

The instant specification enables the claimed invention. The instant claims relate to a simulated metal ion. The claimed invention is not a polyhedron-metalloprotein. (*See* OA at p.

3.) The instant application describes and teaches both zinc and magnesium embodiments (including illustrative force field parameters) of the claimed invention. (Application pp. 7-12.) The application provides working examples (including force field parameters and crystal coordinates) of multiple metalloproteins containing metal ions. (Application pp. 14-25.) The specification recites that "[p]ersons of ordinary skill in the art know how to create and modify molecules and ligands in MD [molecular dynamics] simulation computer programs." (Application p. 7.) In addition, the Specification indicates that, "A person of ordinary skill in the art knows how to identify the appropriate polyhedron arrangement for metals in proteins," and that "polyhedron arrangements for ... metal ions can be derived from known crystal structures and the art in general." (Application at p. 10-11.) The Specification provides specific parameters for tetrahedral zinc, octahedral magnesium, and octahedral calcium coordination complexes. (Application at tables 1, 2 and 3.)

The claims are enabled and the Examiner's rejection is improper. As indicated above, it is incumbent upon the Examiner to provide a detailed and reasoned explanation as to why she doubts the veracity of the instant application to overcome a presumptively enabled application.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 38, 39 and 44 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

With respect to claims 38 and 39, the Examiner observed that no unit was ascribed to the numeral "0.1" describing the mass of the dummy atom. (OA p. 4.) To more particularly point out and distinctly claim the instant subject matter, claims 38, 39 and 44 have been amended to recite the atomic mass unit g/mol. Mass units for chemical elements are terms commonly understood by those of ordinary skill in the art to which this invention belongs. The units are often disregarded because it is commonly understood that chemical element units are equivalently atomic mass units per atom or g/mole. A patent specification need not teach and preferably omits that which is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). The Specification recites that "[u]nless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in

the art to which this invention belongs." (Application at p. 4.) No new matter has been added by these amendments.

With respect to Claim 44, the Examiner observed that the term "main group" does not clearly indicate which elements constitute the claimed invention. Claim 44 has been amended to recite main group metal to more particularly point out and distinctly claim the invention. Support for this amendment can be found throughout the application including pages 4 and 6.

Applicant believes that the Examiner agreed to withdraw her rejections relating to § 112, second paragraph in view of Applicant's amendments during the telephonic interview.

Rejections under 35 U.S.C. § 103

The Examiner has rejected Claims 37-49 and 52-54 under 35 U.S.C. § 103(a) as unpatentable as obvious over Mercandelli et al., (J. Am. Chem. Soc., 1996) ("Mercandelli") in view of Allinger et al., (J. Mol. Struct. (Theochem.), 1994) ("Allinger"). The Examiner asserted that "Mercandelli et al. clearly motivates the simplification of molecular topology by using dummy atoms," and that "the reference states the setting of the metal atom parameters of the Van der Waals interactions to zero..." (OA, p. 5.)

The Examiner bears the burden of establishing a *prima facie* case of obviousness. In re Oetiker, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Ultimately, obviousness requires that the prior art, taken as a whole, fairly suggest the desirability to make the patentee's invention and reveal a reasonable expectation of success. In re Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984); In re Dillon, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Only after both elements are met is a *prima facie* case of obviousness established. The Examiner has failed to establish a *prima facie* case of obviousness and accordingly these rejections should be withdrawn.

Applicant respectfully traverses these rejections. As shown in the graphical illustration below, the Mercandelli teaching and the instant claims are inapposite. Mercandelli teaches substituting a single dummy atom for a multi-atom ligand in molecular mechanics computations. (Mercandelli at p. 11548, right column, last paragraph.) The instant claims recite simulated metal ions having dummy atoms and center atoms for more accurately representing metal ions during molecular dynamics simulations. (*E.g.*, claim 37 as amended.) In sum, Mercandelli teaches that the dummy atom 1) represents an aspect of the ligand NOT the metal atom, 2) is

NOT assigned a charge so that the overall charge of the metal ion is evenly distributed among the dummy atoms, 3) is NOT assigned a mass, and 4) is used in a molecular mechanics computation NOT a molecular dynamics simulation.

Graphical Illustration

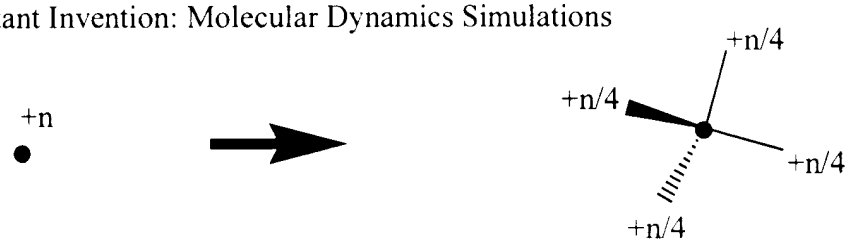
Mercandelli: Molecular Mechanics Computations

multi-atom Ligand

reduce complexity: replace multiple atom interactions with a single dummy atom

resulting single dummy atom Ligand

Instant Invention: Molecular Dynamics Simulations



Metal Ion

increase complexity: add dummy atoms

resulting multi-atom polydedron Metal Ion

Referring to Mercandelli, the purpose for the dummy atom is to provide a "place-holder" for the topology or orientation of a ligand group, *i.e.*, ligands having a face or plane. (Mercandelli at p. 11548, right column, last paragraph, last sentence.) The place-holder provides an easy substitute in a three dimensional space for the average distance and average interactions between the individual atoms of the ligand group and the metal atom. (*See, e.g.*, Mercandelli, Figure 1.) The place-holder does not represent an actual characteristic of the ligand. The place-holder in Mercandelli simplifies the structure by reducing the number of computations needed during a single iteration of a molecular mechanics computation. Molecular mechanics computations evaluate the overall energy of a particular structure using a force field or other potential function. A force field is a sum of individual energies of all atoms of a system. The

force field typically includes bond, angle, torsion, Van Der Waals ("vdW") and electrostatic interactions.

Mercandelli teaches how to simplify certain types of molecular mechanics computations by replacing multiple atoms with a single dummy atom. For example, the five carbon atoms and five hydrogen atoms of the cyclopentadienyl ligand used in Mercandelli are reduced to a single dummy atom place-holder located at the center of the plane of the cyclopentadienyl ligand. (Mercandelli at p. 11548, right column, last paragraph.) As a result, the molecular mechanics computation processes interactions between the dummy atom and a metal atom (*see, e.g.*, Mercandelli, Table 1, D_{Cp} dummy centroids) instead of computing multiple interactions between each of the ligand carbon atoms and each of the hydrogen atoms paired the metal atom (*see, e.g.*, Mercandelli, interactions a and b of Figure 1). In other words, the Mercandelli dummy atom represents an overall average of the forces and locations attributed to each of the atoms of the ligand as the forces and locations apply to the metal atom. As a result, there are fewer computations involved in the molecular mechanics computation.

With all due respect, Applicant submits that the Examiner was mistaken when she also asserted that "Figure 1 (p. 11550) [of Mercandelli] displays a model of a central metal ion and its evenly distributed interaction among dummy atoms: c, d and e." (OA p. 5.) Items c, d, and e are not dummy atoms. Items c, d, and e are not interactions between a dummy atom and another atom. Items c, d, and e of Figure 1 of Mercandelli are 1,3 vdW contact interactions "about," i.e., around, the metal center. (Mercandelli p. 11549, right column, last paragraph & Figure 1.) The 1,3 interactions are vdW interactions between and among ligand ("L") atoms not between ligands and the simulated metal atom in question. Item c is a nonbonded interaction between carbon atoms of two separate cyclopentadienyl ligands; item d is a nonbonded interaction between a carbonyl ligand and a carbon atom of a cyclopentadienyl ligand; and e is a nonbonded interaction between a separate metal atom and a carbon atom of a cyclopentadienyl ligand. The c, d, and e interactions are included so that the structure does not "collapse" on the metal atom. (Mercandelli p. 11549, right column, last paragraph.)

There is an aspect of Mercandelli that requires further explanation. Figure 1 of Mercandelli provides a sketch of the vdW interactions about a metal atom. Figure 1 uses stick-type drawings in the Figure to denote both covalent bonds and noncovalent interactions.

Mercandelli recognizes that visualizing the vdW interactions is difficult and refers the reader to Figure 1 for "further insight." (Mercandelli p. 11549, right column, last paragraph & Figure 1.) As can be seen from Figure 1, the stick-type drawings between "M" and "L"[1] do not represent covalent bonds because it is known that the metal atoms are not covalently bonded to their ligands. This fact is confirmed in Mercandelli because Mercandelli teaches that the vdW interactions between the second metal atom and the carbonyl ligands are considered during the molecular mechanics computation. (*Id.*) Further, Van der Waals interactions are not applicable for covalently bound atoms. On the other hand, the cyclopentadienyl ligands of Figure 1 are represented using the conventional ball and stick drawing with the sticks representing the covalent bonds. As a result, a reader simply does not and cannot know whether the stick-type representations between the metal atom (the "M" on the left in Figure 1) and dummy atoms (point in the middle of cyclopentadienyl groups of Figure 1) are covalent bonds denoting a simulated metal ion having multiple atoms. Applicant submits that a fair reading of Mercandelli suggests that the stick-type drawing between the metal atom and the dummy atoms located in the center of the cyclopentadienyl ligands are NOT covalent bonds because the dummy atoms were generated as atoms of the cyclopentadienyl ligand NOT the metal atom. However, Table 1 gives a force constant for the metal/dummy atom bond, which suggests that there is a covalent bond between the dummy atoms and the metal atom. Even so, Applicant recognizes that without more information Mercandelli is inconclusive on this point.

Applicant submits that if the stick-drawings between the metal atoms and the dummy atoms are not covalent bonds, Mercandelli does not teach or even remotely suggest a simulated metal ion having multiple atoms because the metal atom is but one atom. And, even if for the sake of argument the stick-drawings between the metal atom and the dummy atoms in Figure 1 are considered covalent bonds, Mercandelli still does not teach or reasonably suggest the claimed invention for two principle reasons. (*Please refer to* claim 37 as amended.) First, the dummy atoms are not assigned a charge so that the overall charge of the metal ion is evenly distributed among the dummy atoms. Second, the dummy atom is not assigned a mass.

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[1] Applicant interprets "L" in Figure 1 to be the carbonyl ligands.

Nevertheless regardless of the status of the linkage (if there is any), between the dummy atom and the left metal atom in Figure 1 of Mercandelli, the instant invention is inapposite from the teachings of Mercandelli for at least the following reasons. First, the claimed invention recites a simulated metal ion. Mercandelli teaches simulating the ligand by using a place-holder for the Ligand's ring structure. Second, the claimed invention assigns a charge to the dummy atoms to represent the charge distribution of the metal ion. Mercandelli does not assign a charge to the dummy atom. To the extent that the Mercandelli article does consider charge, it would be the charge of the ligand not the metal ion. The dummy atoms of Applicant's claimed invention represent the vacant electronic orbitals of a metal ion itself, and the charge of the metal ion are ascribed to the dummy atoms. Third, the claimed invention is directed to simulating metal ions in molecular dynamics simulations, which requires that the atoms be assigned a mass. Mercandelli does not teach assigning a mass to the dummy atom. Each of the distinctions identified above are found in the instant claims and only the instant claims.

Applicant does not dispute that it is proper for the Examiner to consider Allinger with Mercandelli. As noted by the Examiner, Mercandelli refers to and uses the vdW parameters of Allinger. (OA at p. 5; Mercandelli footnote 15.) Allinger, however, does not remedy the deficiencies of Mercandelli highlighted above. Allinger simply provides certain known parameters for metal ions, and other atoms, for use in molecular mechanics computations. Allinger taken alone or in view of Mercandelli does not teach or suggest simulating a metal ion as claimed in the instant application. For example, there is no suggestion of a multi-atom metal ion having a center atom having a van der Waals radius greater than zero covalently linked to one or more dummy atoms having a van der Waals radius of about zero, wherein the overall charge of the metal ion is evenly distributed among the dummy atoms and wherein the center atom has a charge of zero. References used in an obviousness rejection, when combined, must arrive at the invention. These references do NOT arrive at the claimed invention.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 37-54 under 35 U.S.C. § 103(a) as being unpatentable over Mercandelli et al. in view of Allinger et al., as applied to claims 37-49 and 52-54, and further in view of Alberts et al., (Protein Science, 1998) ("Alberts") and Stote et al. (Proteins,

1995) ("Stote"). (OA p. 5.) The Examiner wrote "Mercandelli et al. in view of Allinger suggests the basic invention; while Alberts et al. further describes the polyhedron and Stote et al. further describes the solvation energy considerations in such inventions." (OA, p.6.)

Applicant traverses these rejections for the reasons stated above and for the additional reasons set forth below. Principally, Applicant submits that it is improper to combine the references relied upon by the Examiner, and even if combined, the cited references do not teach or reasonably suggest the claimed invention.

The Examiner has failed to satisfy her burden of identifying a suggestion to combine Alberts and/or Stote with Mercandelli and Alberts. As the Federal Circuit has recently stated:

> We have previously held that "[t]he suggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved." WMS Gaming, Inc. v. International Game Tech., 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). However, there still must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." In re Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1456; see also In re Werner Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("[A] rejection cannot be predicated on the mere identification . . . of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.").

Ecolochem, Inc. v. Southern California Edison Co., No. 99-1043, 2000 WL 1273566 at *12 (Fed. Cir. (Cal.) Sept. 7, 2000).

Further, the instant claims are patentable even if Alberts and/or Stote were combined with Mercandelli and Allinger. As discussed above, Mercandelli taken alone or in view of Allinger does not teach or reasonably suggest a simulated metal ion for use in a molecular dynamics simulation having: 1) a center atom having a van der Waals radius greater than zero, 2) covalently linked to one or more dummy atoms having a van der Waals radius of about zero, 3) wherein the overall charge of the metal ion is evenly distributed among the dummy atoms, and 4) wherein the center atom has a charge of zero.

Alberts merely reports the geometrical properties of zinc binding sites in a dataset of protein crystal structures. (Alberts p. 1700.) Alberts reports that by analyzing known crystal

structures a person can arrive at an aid for "validating" zinc binding sites in molecular models. (*Id.* p. 1714, right column.) Such a disclosure does not suggest the instant invention. Applicant submits that one of the dilemmas of known molecular models is that they did not sufficiently validate the metal coordination complexes actually observed in crystal structures. (*See* Application at p. 1.) Moreover, disclosing that the end result of a modeling program should be that of the structure actually observed does not suggest a way to arrive at the end result.

The addition of Stote does not remedy the deficiencies of any of the previously discussed references, i.e., Mercandelli, Allinger, and Alberts, either alone or together. Stote indicates that force field parameters should and/or can be considered during a molecular dynamics simulation. Stote acknowledges the deficiencies of known modeling methods, e.g., bonded and nonbonded methods. (Stote pp. 12-13.) Yet, Stote teaches using a conventional nonbonded model, albeit one that is "carefully parameterized." (*Id.* p. 13, left column, last paragraph.) The suggested parameters do not suggest or remedy the explicit elements of claim 37 that are missing from each and every one of the references cited by the Examiner, either alone or taken together. Stote does not suggest adjusting vdW parameters, does not suggest using dummy atoms having a charge, or using multi atom metal ions as found in the instant claims.

It is incumbent upon the Examiner to provide a reasoned explanation of where in one or more of the cited references there is a suggestion of a simulated metal ion for use in a molecular dynamics simulation having: 1) a center atom having a van der Waals radius greater than zero, 2) covalently linked to one or more dummy atoms having a van der Waals radius of about zero, 3) wherein the overall charge of the metal ion is evenly distributed among the dummy atoms, and 4) wherein the center atom has a charge of zero. Further, the Examiner must identify specific reasons why a skilled artisan (without having the instant application as a road map) would be motivated to combine the references to arrive at the instant invention. Conclusory statements that certain features identified in the cited references should be used in molecular modeling programs does not satisfy the Examiner's burden.

Accordingly, the Examiner's rejections are improper.

Conclusion

Applicant's claimed invention is a novel and nonobvious way to simulate metal ions in molecular dynamics simulations wherein the metal ions have: 1) a center atom having a van der Waals radius greater than zero, 2) covalently linked to one or more dummy atoms having a van der Waals radius of about zero, 3) wherein the overall charge of the metal ion is evenly distributed among the dummy atoms, and 4) wherein the center atom has a charge of zero.

In light of the above Amendments and Remarks, Applicant submits that the claims are in condition for allowance. Reconsideration of the Examiner's rejections and prompt allowance of all claims is respectfully requested. Enclosed is a $55.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 12/17/01

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Version with markings to show changes made

In the claims:

Claims 37-54 have been amended, and claims 55-72 have been added as follows:

37. (amended) A computer readable medium having data structures stored thereon, comprising a data structure to store a simulated metal ion [molecule] for use in a molecular dynamics simulation comprising a center atom having a van der Waals radius greater than zero covalently linked to one or more dummy atoms having a van der Waals radius of about zero, wherein the overall charge of said metal ion [molecule] is evenly distributed among said dummy atoms and wherein said center atom has a charge of zero.

38. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said dummy atom has a mass of about 0.1 g/mol.

39. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said dummy atom has a mass greater than about 0.1 g/mol.

40. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said dummy atoms are located at the apices of a polyhedron.

41. (amended) The computer readable medium [simulated metal ion molecule] of claim 40 wherein said center atom is located at the center of said polyhedron.

42. (amended) The computer readable medium [simulated metal ion molecule] of claim 40 wherein said polyhedron is selected from the group consisting of trigonal, tetrahedron, pentahedron, hexagonal, septagonal, and octahedral.

43. (amended) The computer readable medium [simulated metal ion molecule] of claim 41 wherein said polyhedron is a tetrahedron.

44. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said metal ion is selected from a main group metal or transition metal.

45. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said metal ion is selected from the group consisting of zinc, cadmium, mercury, copper, nickel, cobalt, iron, manganese, calcium, and magnesium.

46. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said metal ion is zinc.

47. (amended) The computer readable medium [simulated metal ion molecule] of claim 41 wherein said metal ion is zinc.

48. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said metal ion is magnesium.

49. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said metal ion is calcium.

50. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said metal ion has a calculated energy of solvation about equal to an experimentally determined energy of solvation for said metal ion.

51. (amended) The computer readable medium [simulated metal ion molecule] of claim 50 wherein said calculated energy of solvation is within about 10% of said experimentally determined energy of solvation for said metal ion.

52. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said dummy atom has a charge of about 0.5.

53. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said dummy atom has a charge of about 0.3333.

54. (amended) The computer readable medium [simulated metal ion molecule] of claim 37 wherein said dummy atom has a charge ranging from about +0.1 to about +3.

55. (new) A computer readable medium having computer executable instructions stored thereon, that when executed simulate a metal ion for use in a molecular dynamics simulation comprising a center atom having a van der Waals radius greater than zero covalently linked to one or more dummy atoms having a van der Waals radius of about zero, wherein the overall charge of said metal ion is evenly distributed among said dummy atoms and wherein said center atom has a charge of zero.

56. (new) The computer readable medium of claim 55 wherein said dummy atom has a mass of about 0.1 g/mol.

57. (new) The computer readable medium of claim 55 wherein said dummy atom has a mass greater than about 0.1 g/mol.

58. (new) The computer readable medium of claim 55 wherein said dummy atoms are located at the apices of a polyhedron.

59. (new) The computer readable medium of claim 58 wherein said center atom is located at the center of said polyhedron.

60. (new) The computer readable medium of claim 58 wherein said polyhedron is selected from the group consisting of trigonal, tetrahedron, pentahedron, hexagonal, septagonal, and octahedral.

61. (new) The computer readable medium of claim 59 wherein said polyhedron is a tetrahedron.

62. (new) The computer readable medium of claim 55 wherein said metal ion is selected from a main group metal or a transition metal.

63. (new) The computer readable medium of claim 55 wherein said metal ion is selected from the group consisting of zinc, cadmium, mercury, copper, nickel, cobalt, iron, manganese, calcium, and magnesium.

64. (new) The computer readable medium of claim 55 wherein said metal ion is zinc.

65. (new) The computer readable medium of claim 59 wherein said metal ion is zinc.

66. (new) The computer readable medium of claim 55 wherein said metal ion is magnesium.

67. (new) The computer readable medium of claim 55 wherein said metal ion is calcium.

68. (new) The computer readable medium of claim 55 wherein said metal ion has a calculated energy of solvation about equal to an experimentally determined energy of solvation for said metal ion.

69. (new) The computer readable medium of claim 68 wherein said calculated energy of solvation is within about 10% of said experimentally determined energy of solvation for said metal ion.

70. (new) The computer readable medium of claim 55 wherein said dummy atom has a charge of about 0.5.

71. (new) The computer readable medium of claim 55 wherein said dummy atom has a charge of about 0.3333.

72. (new) The computer readable medium of claim 55 wherein said dummy atom has a charge ranging from about +0.1 to about +3.